PCT
REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* ARSB523P

Box No. I TITLE OF INVENTION
PROMOTER FOR SMOOTH MUSCLE CELL EXPRESSION

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

ARCH DEVELOPMENT CORPORATION
1101 EAST 58TH ST.
CHICAGO, IL 60637
UNITED STATES OF AMERICA

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

PARMACEK, Michael S.
1225 East 56th Street
Chicago, IL 60637
United States of America

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by give name; for a legal entity, full official designation. The address must include postal code and name of country.)*

CORDER, Timothy S.
ARNOLD, WHITE & DURKEE
P.O. Box 4433
Houston, TX 77210
United States of America

Telephone No. (512) 418-3000

Facsimile No. 713-789-2679

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

SOLWAY, Julian
746 Grove Street
Glencoe, IL 60022
United States of America

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: US

State *(i.e. country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

This person is:
☐ applicant only
☐ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

This person is:
☐ applicant only
☐ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated Sates except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

This person is:
☐ applicant only
☐ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☒ **AP ARIPO Patent:** GH Ghana, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒AL Albania
☒AM Armenia
☒AT Austria
☒AU Australia
☒AZ Azerbaijan
☒BA Bosnia and Herzegovina
☒BB Barbados
☒BG Bulgaria
☒BR Brazil
☒BY Belarus
☒CA Canada
☒CH and LI Switzerland and Liechtenstein
☒CN China
☒CU Cuba
☒CZ Czech Republic
☒DE Germany
☒DK Denmark
☒EE Estonia
☒ES Spain
☒FI Finland
☒GB United Kingdom
☒GE Georgia
☒GH Ghana
☒HU Hungary
☒IL Israel
☒IS Iceland
☒JP Japan
☒KE Kenya
☒KG Kyrgyzstan
☒KP Democratic People's Republic of Korea
☒KR Republic of Korea
☒KZ Kazakhstan
☒LC Saint Lucia
☒LK Sri Lanka
☒LR Liberia
☒LS Lesotho
☒LT Lithuania
☒LU Luxembourg
☒LV Latvia
☒MD Republic of Moldova
☒MG Madagascar
☒MK The former Yugoslav Republic of Macedonia
☒MN Mongolia
☒MW Malawi
☒MX Mexico
☒NO Norway
☒NZ New Zealand
☒PL Poland
☒PT Portugal
☒RO Romania
☒RU Russian Federation
☒SD Sudan
☒SE Sweden
☒SG Singapore
☒SI Slovenia
☒SK Slovakia
☒SL Sierra Leone
☒TJ Tajikistan
☒TM Turkmenistan
☒TR Turkey
☒TT Trinidad and Tobago
☒UA Ukraine
☒UG Uganda
☒US United States of America (CIP)
☒UZ Uzbekistan
☒VN Viet Nam
☒YU Yugoslavia
☒ZW Zimbabwe

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

☐ .....
☐ .....
☐ .....
☐ .....

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designations(s) of _____. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet need not be included in the request.*

Use this box in the following cases:

1. If, in any of the Boxes, the space is insufficient to furnish all the information:	*in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient;*
in particular:	
(i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available:	*in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (i.e., country) of residence if no State of residence is indicated below:*
(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked:	*in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*
(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America:	*in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named persons is inventor;*
(iv) if, in addition to the agent(s) indicated in box No. Iv, there are further agents:	*in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*
(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "Continuation" or "Continuation-in-part":	*in such case, write "Continuation of Box V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*
(vi) if there are more than three earlier applications whose priority is claimed:	*in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*
2. If the applicant claims, in respect of any designated Office, the benefits, of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty:	***in such case, write "Statement Concerning Non-Prejudicial Disclosures or Exceptions to Lack of Novelty: and furnish that statement below.***

CONTINUATION OF BOX V 08/726.807 filed October 7, 1996

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country *(in which, or for which, the application was filed)*	Filing Date *(day/month/year)*	Application No.	Office of filing *(only for regional or international application)*
item (1) US	07 OCTOBER 1996 (07.10.1996)	08/726.807	
item (2)			
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): 1

BOX No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA / EPO

Earlier search *Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:*

Country (or regional Office):	Date:	Number:
US	07 OCTOBER 1996 (07.10.96)	08/726.807

BOX No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	: 5 sheets
2. description	: 78 sheets
3. claims	: 7 sheets
4. abstract	: 1 sheets
5. drawings	: 2 sheets
Total:	: 93 sheets

This international application is accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney
2. ☐ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. ☐ priority document(s) *(identified in Box No. VI as item(s):*
5. ☒ fee calculation sheet
6. ☐ separate indications concerning deposited microorganisms
7. ☒ nucleotide and/or amino acid sequence listing (diskette)
8. ☒ other (specify): **post card, Statement of Conformity**

Figure No. _____ of the drawing (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Timothy S. Corder

For receiving Office use only

1. Date of actual receipt of the purported international application:

2. Drawings:

3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:

[ ] received:

[ ] not received

4. Date of timely receipt of the required corrections under PCT Article 11(2):

5. International Searching Authority specified by the applicant: ISA/

6. [ ] Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GRÜNECKER, KINKELDEY, STOCKMAIR & PARTNER
Maximilianstrasse 58
D-80538 München
ALLEMAGNE

GRÜNECKER, KINKELDEY, STOCKMAIR & SCHWANHÄUSSER ANWALTSSOZIETÄT
- 2. Nov. 1998
FRIST TERM 29.12.98
EINGANG-RECEIVED

PCT

WRITTEN OPINION

(PCT Rule 66)

10

Date of mailing (day/month/year)	29.10.98
REPLY DUE	within **2 month(s)** from the above date of mailing

Applicant's or agent's file reference		
PCT 867-031/ld		
International application no.	**International filing date** *(day/month/year)*	**Priority date** *(day/month/year)*
PCT/US97/16204	29/08/1997	07/10/1996

International Patent Classification (IPC) or both national classification and IPC
C07K14/47

Applicant
ARCH DEVELOPMENT CORPORATION et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This report contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and / or arguments, see Rule 66.4bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 07/02/1999

Name and mailing address of the international preliminary examining authority
European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer / Examiner
Heckl, K

Formalities officer (incl. extension of time limits)
Peralt Lappas, R
Telephone No. (+49-89) 2399-8052

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-78	as originally filed				

Claims, No.:

1-51	as received on	20/10/1998	with letter of	20/10/1998	

Drawings, sheets:

1-3	as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 6,12,24,30,35,

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 6,12,24,30,35.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-51
Inventive step (IS)	Claims	1-51
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

ad section III

1. No ISR has been established for the subject-matter of claims 6, 12 , 24, 30 and 35. Accordingly, these claims have been subjected to IPE only partially, i.e. as far as specified by the characterizing features of claims 7, 9, 11, 25-29, 42 and 44.

ad section V

1. The following documents are considered relevant prior art:

D1: J. Biol. Chem. 270/22, 02.06.96, 13460-69
D2: J. Cell Biol. 01.03.96, 849-59
D3: Development 122, 01.05.96, 2415-25
D4: Biochem. J. 310, 1995, 1037-43
D5: WO94/11506
D6: Science 267, 1995, 518-22
D7: EP-A2-0 666 270
D8: WO96/26742

2. Novelty (Art.33(2) PCT):

2.1 The cited prior art discloses studies on the in vivo expression pattern of the SM22 alpha gene by using the SM22 alpha promoter in various forms driving the expression of a detectable marker (such as the luciferase, the lacZ or the CAT gene), vectors and hosts comprising these constructs , (see D1, abstract and "plasmids"; D2, abstract, "generation of ... Reporters", "generation of transgenic mice"; D3, abstract and "reporter constructs"; D4, abstract, "determination of promoter activity" and discussion).

2.2 Accordingly, the subject-matter of claims 1-5, 13, 14 and 19-22 is not novel.

3. Inventiveness (Art.33(3) PCT):

3.1 The general idea underlying the claims is the tissue specific expression of therapeutic genes in order to treat cell proliferation diseases such as

atherosclerosis, restenosis following balloon angioplasty and airway blockage in asthma (see the description, page 1, lines 9-12).

The problem has already been solved in the prior art by applying an adenovirus construct comprising **"a cardiac muscle specific enhancer-promoter"** which is "specific for vascular SM" such as the SM alpha-actin promoter (see D5, claims 1, 7, 9 and 10).

3.2 Accordingly, it was the problem underlying the claims to select an other promoter specific for SMC. In order to solve the problem posed the skilled person would turn to any of documents D1 to D4, which disclose the SM22 alpha promoter to direct lineage specific gene expression in SMCs.

In addition, both D2 and D3 disclose this promoter as **"to offer an opportunity to genetically manipulate the physiology and pathology of the cardiovascular system..."** (see D2, last paragraph; D3 , last paragraph) and hence encourage the skilled person to apply the same in combination with cell cycle control genes, angiogenesis genes, cytotoxic genes or antisense constructs.

In fact, such genes are well known in this field, such as disclosed in D5, claims 18 and 22; D6, abstract; D7, claims 1-30; and D8, claim 10.

3.3 Accordingly, the subject-matter of claims 6-12, 15-18 and 23-51 lacks an inventive step.

EPA/EPO/OEB
D-80298 München
(089) 2399-0
TX 523 656 epmu d
FAX (089) 2399-4465

Correspondence with the EPO on PCT Chapter II demands

In order to ensure that your PCT Chapter II demand is dealt with as promptly as possible you are requested to use the enclosed self-adhesive labels with any correspondence relating to the demand sent to the Munich Office.

One of these labels should be affixed to a prominent place in the upper part of the letter or form etc. which you are filing.

PATENT COOPERATION TREATY

om the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GRÜNECKER, KINKELDEY, STOCKMAIR &
PARTNER
Maximilianstrasse 58
D-80538 München
ALLEMAGNE

GRÜNECKER, KINKELDEY, STOCKMAIR
& SCHWANHÄUSSER
ANWALTSSOZIETÄT
17. Feb. 1999
EINGANG - RECEIVED

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	15.02.99
Applicant's or agent's file reference PCT 867-031/ld	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US97/16204	29/08/1997	07/10/1996

Applicant
ARCH DEVELOPMENT CORPORATION et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Heisel, M Tel. (+49-89) 2399-8051

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
PCT 867-031/ld		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US97/16204	29/08/1997	07/10/1996
International Patent Classification (IPC) or national classification and IPC		
C07K14/47		
Applicant		
ARCH DEVELOPMENT CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07/05/1998	15.02.99
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0. Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Heckl, K Telephone No. (+49-89) 2399-8430

Form PCT/IPEA/409 (Cover sheet) (January 1994)

ERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US97/16204

I. Basis of the r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-78 as originally filed

Claims, No.:

1-49 as received on 04/01/1999 with letter of 04/01/1999

Drawings, sheets:

1-3 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 6,12,22,33,36,41,44 and 45 part..

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 44 and 45 part. are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 6,12,22,33,36,41.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-49
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-49
Industrial applicability (IA)	Yes:	Claims	1-49
	No:	Claims	

2. Citations and explanations

see separate sheet

ad section I

1. Claim 36 does not contain the feature of "wherein expression of said cell cycle regulatory gene inhibits proliferation of said smooth muscle cell" as referred to in corresponding and originally filed claim 40. In order to allow the IPE of claim 36 it is assumed that this feature was accidently omitted and should be present in claim 36.

ad section III

1. No ISR has been established for the subject-matter of claims 6, 12 , 26, 32 and 37 as originally filed. These claims now correspond to claims 6, 12, 22, 33, 36, 41 and 49. Accordingly, these claims have been subjected to IPE only partially, i.e. as far as specified by the characterizing features of claims 7, 8, 10, 11, 23-26 and 40.

2. Claims 44 and 45 refer to the expression in coronary and peripheral **arterial** and **venous** SMC. In contrast, the prior discloses "the transgene expression as not detectable in venous nor visceral SMCs" (see D2, abstract; D3 title and abstract). However, neither claims 44 and 45, nor independent claim 43 identify features which seem responsible for this observed difference to the prior art. It is also to be noted that the same applied to the features of claims 1-5 which claim SM22 alpha promoter elements identical or equivalent to those of D1-D4 (see below, section V).

   Therefore, claims 44 and 45 as far as referring to the expression in coronary and peripheral **venous** SMC cannot be subjected to IPE.

ad section V

1. The following documents are considered relevant prior art:

   D1: J. Biol. Chem. 270/22, 02.06.96, 13460-69
   D2: J. Cell Biol. 01.03.96, 849-59
   D3: Development 122, 01.05.96, 2415-25
   D4: Biochem. J. 310, 1995, 1037-43

D5: WO94/11506
D6: Science 267, 1995, 518-22
D7: EP-A2-0 666 270
D8: WO96/26742

It is indicated that document WO9735974 which has been classified as E document represents relevant prior art in the EP phase of this application.

2. Novelty (Art.33(2) PCT):

2.1 The cited prior art discloses studies on the in vitro and in vivo expression pattern of the SM22 alpha gene by using the SM22 alpha promoter in various forms driving the expression of a detectable marker (such as the luciferase, the lacZ or the CAT gene), vectors and hosts comprising these constructs , (see D1, abstract and "plasmids"; D2, abstract, "generation of ... Reporters", "generation of transgenic mice"; D3, abstract and "reporter constructs"; D4, abstract, "determination of promoter activity" and discussion).

2.2 By disclaiming the SM22 alpha - reporter gene constructs of the prior art (see above, item 2.1) the subject-matter of the claims is rendered novel.

3. Inventiveness (Art.33(3) PCT):

3.1 The concept underlying claims 1-5 is to take use of the SM22 alpha promoter to drive heterologous gene expression in a tissue specific manner.

However, this tissue specific manner has been disclosed in the prior art including the characterization of various promoter fragments within this respect (see above, D1-D4 as cited). Moreover, these fragments are clearly in the range of those comprised in claims 1-5 and the differences seem to reside within the variation of routine experimentation which cannot contribute to inventiveness.

Therefore, the subject-matter of claims 1-5 cannot be considered inventive.

3.2 The general idea underlying the claims 6-17 is the tissue specific expression of

therapeutic genes in order to treat cell proliferation diseases such as atherosclerosis, restenosis following balloon angioplasty and airway blockage in asthma (see the description, page 1, lines 9-12).

3.3 Any of documents D2 or D3 is considered closest prior art within this respect. In addition to the above identified disclosure (see above, item 2.1), D2 and D3 disclose the isolated SM22 alpha promoter as "to offer an opportunity to genetically manipulate the physiology and pathology of the cardiovascular system by directing genes involved in cell growth and differentiation into the cardiovascular system" (see D2, last paragraph) and as "to raise interesting possibilities of applying gene therapy following arterial injury" (D3 , last paragraph).

Therefore, it was the problem underlying claims 6-17 to select particular genes for this purpose. Clearly, such genes are well known in this field, such as disclosed in D5, claims 18 and 22; D6, abstract; D7, claims 1-30; and D8, claim 10.

Therefore, the subject-matter of claims 6-17 cannot be considered inventive, either.

3.4 The same applies to the subject-matter of claims 18-49. It should be noted in this context that neither the particular selection of the host cell, nor the choice of a replication deficient adenoviral vector as the construct can contribute to inventiveness (see D1, abstract; D5, page 3, line 29 to page 4, line 28; D6, abstract and the passage bridging pages 518 and 519; D8, abstract).

3.5 The methods of claims 30-35, 36-40, 41-48 and 49 are also the outcome of the above considerations applied by the skilled person.

3.6 It should be noted in this context that the problem as defined above (see item 3.3) has already been solved in the prior art by applying an adenovirus construct comprising "**a cardiac muscle specific enhancer-promoter**" which is "specific for vascular SM" such as the SM alpha-actin promoter (see D5, claims 1, 7, 9 and 10).

Starting form this aspect, it was the problem underlying claims 6-49 to select an other promoter specific for SMC. In order to solve the problem posed the skilled person would turn to any of documents D1 to D4, which disclose the SM22 alpha promoter to direct lineage specific gene expression in SMCs. This applies all the more since documents D2 and D3 clearly suggest the use of the SM22 alpha promoter for this purpose (see above, item 3.3).

3.7 Inventiveness of claims 44 and 45

As outlined above, the expression in coronary and peripheral arterial SMC is rendered obvious from D1-D3. Again, D1 discloses "the 441 base pairs of SM22 alpha 5'-flanking sequence necessary and sufficient to program high level transcription ... in both primary rat aortic SMCs and A7r5 cells" (see the abstract). Similar results are reported by D2 ("... sufficient to direct the expression ... in mouse embryos in the vascular smooth, cardiac, and skeletal muscle lineages ... similar to that of the endogenous SM22 alpha gene", see the abstract), and by D3 ("... the SM22 promoter activity persisted in the SMCs of arteries", see the abstract) .

Therefore, claims 44 and 45 as far as referring to the expression in coronary and peripheral **arterial** SMC cannot be considered inventive.

4. For the assessment of the present claims 39-49 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

CLAIMS

1. A recombinant vector comprising an isolated nucleic acid segment comprising an SM22α promoter, wherein said promoter is within a segment of about 5,000 bases immediately upstream of the transcriptional start site of the murine SM22α gene and wherein said promoter is operatively linked to a heterologous nucleic acid sequence,

   with the proviso that said heterologous nucleic acid is not coding for luciferase, β-galactosidase or chloramphenicol acetyl transferase.

2. The recombinant vector of claim 1, wherein the isolated nucleic acid segment is further defined as comprising a nucleic acid segment having a sequence according to bases 899-1382 of SEQ ID NO:1, or being hybridizable to the complement of bases 899-1382 of SEQ ID NO:1 under high stringency conditions, and effective to promote transcription of a heterologous gene in a smooth muscle cell.

3. The recombinant vector of claim 1, wherein said promoter sequence is further defined as comprising a contiguous sequence of bases 899-1382 of SEQ ID NO:1.

4. The recombinant vector of claim 1, wherein said promoter sequence is further defined as comprising a contiguous sequence of bases 1-1382 of SEQ ID NO:1.

5. The recombinant vector of claim 1, wherein said promoter sequence is further defined as comprising a contiguous sequence of bases 1060-1382 of SEQ ID NO:1.

6. The recombinant vector of claim 1, wherein said heterologous nucleic acid sequence encodes a cell cycle control gene, an angiogenesis gene or a cytotoxic gene.

7. The recombinant vector of claim 6, wherein said cell cycle control gene is selected from the group consisting of Rb, a phosphorylation deficient Rb gene, p53, p21, p16, p27, a cell cycle dependent kinase inhibitor, E2F inhibitor, a CDK kinase or a cyclin gene.

8. The recombinant vector of claim 6, wherein said cell cycle control gene is a phosphorylation deficient Rb gene, p53, p21 or p16.

9. The recombinant vector of claim 6, wherein said angiogenesis gene is VEGF. iNOS, eNOS, basic FGF or FGF-5.

10. The recombinant vector of claim 6, wherein said angiogenesis gene is VEGF, iNOS or eNOS.

11. The recombinant vector of of claim 6, wherein said cytotoxic gene is a *Herpes simplex* thymidine kinase gene.

12. The recombinant vector of claim 6, wherein said heterologous nucleic acid sequence encodes an antisense RNA effective to inhibit expression of a cell cycle control gene.

13. The recombinant vector of any one of claim 1 to 12 further defined as a plasmid.

14. The recombinant vector of any one of claims 1 to 12, further defined as a viral vector.

15. The recombinant vector of claim 14, wherein said viral vector is a bacteriophage vector, a raus sarcoma virus vector, a p21 virus vector, an adeno-associated virus vector or an adenoviral vector.

16. The recombinant vector of claim 15, wherein said vector is a replication defective adenovirus vector.

17. The recombinant vector of any one of claims 1 to 12, dispersed in a pharmaceutically acceptable solution.

18. A host cell wherein said cell contains the recombinant vector of any one of claims 1 to 17.

19. The host cell of claim 18, wherein said host cell is a smooth muscle cell.

20. The host cell of claim 19, wherein said cell is an A7r5 cell.

21. A replication deficient adenoviral vector, wherein said vector comprises a smooth muscle cell specific transcriptional regulatory segment, wherein said vector comprises an SM22α promoter segment operatively linked to a heterologous gene.

22. The vector of claim 21, wherein said heterologous gene encodes a cell cycle control gene, an angiogenesis gene or a cytotoxic gene.

23. The vector of claim 22, wherein said cell cycle control gene is selected from the group consisting of Rb, a phosphorylation deficient Rb gene, p53, p21, p16, p27, a cell cycle dependent kinase inhibitor, E2F inhibitor, a CDK kinase or a cyclin gene.

24. The vector of claim 22, wherein said cell cycle control gene is a phosphorylation deficient Rb gene, p53, p21 or p16.

25. The vector of claim 22, wherein said angiogenesis gene is VEGF, iNOS, eNOS, basic FGF or FGF-5.

26. The vector of claim 22, wherein said angiogenesis gene is VEGF, iNOS or eNOS.

27. The vector of claim 22, wherein said cytotoxic gene is a *herpes simplex* thymidine kinase gene.

28. The vector of claim 22, wherein said heterologous nucleic acid sequence encodes an antisense RNA effective to inhibit expression of a cell cycle control gene.

29. The vector of claim 21, wherein said vector is dispersed in a pharmacologically acceptable solution.

30. A method of expressing a heterologous gene in a smooth muscle cell comprising the steps of:

(a) obtaining a nucleic acid segment comprising a murine SM22α promoter region operatively linked to a heterologous gene, wherein said nucleic acid is contained in an adenoviral vector;

(b) infecting said smooth muscle cell with said adenoviral vector; and

(c) culturing said smooth muscle cell under conditions effective to express said gene.

31. The method of claim 30, wherein said SM22α promoter comprises bases 899-1382 of SEQ ID NO: 1.

32. The method of claim 30, wherein said heterologous gene is a reporter gene.

33. The method of claim 30, wherein said gene is a cell cycle control regulatory gene.

34. The method of claim 30, wherein said adenoviral vector is a replication deficient adenoviral vector.

35. The method of claim 34, wherein said cell is in an animal and said vector is administered to said animal in a pharmacologically acceptable solution.

36. A method of inhibiting smooth muscle cell proliferation comprising the steps of:

(a) obtaining an isolated nucleic acid segment comprising a cell cycle regulatory gene operatively linked to an SM22α promoter region;

(b) transferring said nucleic acid segment into a smooth muscle cell; and

(c) maintaining said smooth muscle cell under conditions effective to express said cell cycle regulatory gene;

37. The method of claim 36, wherein said smooth muscle cell is in an animal.

38. The method of claim 36, wherein said cell cycle regulator gene operatively linked to an SM22α promoter region comprises a viral or plasmid vector.

39. The method of claim 38, wherein said viral vector is an adenoviral vector.

40. The method of claim 39, wherein said cell cycle regulatory gene is selected from the group consisting of Rb, a phosphorylation deficient Rb gene, p53, p21, p16, p27, a cell cycle dependent kinase inhibitor, E2F inhibitor, a CDK kinase or a cyclin gene.

41. A method of preventing restenosis in a subject following balloon angioplasty, comprising the steps of:

(a) obtaining an adenoviral vector comprising a cell cycle regulatory gene operatively linked to an SM22α promoter region dispersed in a pharmaceutically acceptable solution; and

(b) administering said solution to said subject.

42. The method of claim 41, wherein said cell cycle regulatory gene encodes a constitutively active Rb gene product.

43. A method of promoting angiogenesis in a subject comprising the steps:

(a) obtaining a nucleic acid segment comprising an angiogenesis factor gene operatively linked to an SM22α promoter region; and

(b) transferring said nucleic acid segment into a smooth muscle cell to obtain a transfected cell;

wherein expression of said nucleic acid segment in said smooth muscle cell promotes angiogenesis.

44. The method of claim 43, wherein said smooth muscle cell is a coronary arterial or venous smooth muscle cell.

45. The method of claim 43, wherein said smooth muscle cell is a peripheral arterial or venous smooth muscle cell.

46. The method of claim 43, wherein said angiogenesis factor is VEGF.

47. The method of claim 43, wherein said nucleic acid segment comprising an angiogenesis factor gene operatively linked to an SM22α promoter region is contained in a viral or plasmid vector and said vector is administered to said subject.

48. The method of claim 34, wherein said transferring is done *ex vivo* and the method further comprises the steps:

(a) seeding a bioprosthetic graft or stent with said transfected cells to obtain a seeded graft or stent; and

(b) placing the seeded graft or stent into a coronary or peripheral artery or vein of a subject.

49. A method of inhibiting smooth muscle proliferation comprising the steps of:

(a) obtaining a nucleic acid segment comprising a cell cycle regulatory gene operatively linked to an SM22α promoter region;

(b) transferring said nucleic acid segment into a primary smooth muscle cell *ex vivo* to obtain a transfected cell;

(c) seeding a bioprosthetic graft or stent with said transfected cell to obtain a seeded graft or stent; and

(d) placing the seeded grafted or stent into a coronary or peripheral artery or vein of a subject;

wherein expression of said cell cycle regulatory gene inhibits proliferation of a smooth muscle cell.

[redacted]NT COOPERATION TREATY

STU

Fr m the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
ARNOLD, WHITE & DURKEE
Attn. CORDER T.S.
P.O. Box 4433
Houston, TX 77210
UNITED STATES OF AMERICA

REC'D. - A. W. & D.
FEB 16 1998
INTERNATIONAL DEPT.

RECEIVED
INT'L DEPT.
FEB 17 1998

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference ARSB523P A.W. & D. AUSTIN	Date of mailing *(day/month/year)* 11.02.98 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 97/16204	International filing date *(day/month/year)* 29/08/1997
Applicant ARCH DEVELOPMENT CORPORATION et al	U.S. case ARSB510---docketed File Foreign Search for 3-11-98 by [redacted].

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicants's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Falk Heck

Form PCT/ISA/220 (January 1994)

[redacted]ENT COOPERATION TREAT

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
ARSB523P		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 97/ 16204	29/08/1997	07/10/1996
Applicant		
ARCH DEVELOPMENT CORPORATION et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [X] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [X] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

tional application No.
PCT/US 97/16204

Box I Observation where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 6,12,26,32 and 37

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The claims are too broad, they refer to 'heterologous nucleic acid sequences encoding a cell cycle control gene, an angiogenesis gene or a cytotoxic gene'. The search was limited to cell cycle control genes as specified in claim 7, angiogenesis genes as specified in claim 9 or cytotoxic genes as specified in claim 11.

Remark : Although claims 39-53
are directed to a method of treatment of
the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted] 97/16204

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. SOLWAY ET AL., : "Structure and expression of a smooth muscle cell-specific gene, SM22 alpha" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 270, no. 22, 2 June 1996, BETHESDA, MD,US, pages 13460-13469, XP000609071 cited in the application see the whole document and specially figure 1B	1-5,35
Y		1,7,8, 13-17, 19-21, 23-25, 27,28, 33-36, 38,39

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 January 1998	11.02.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mateo Rosell, A.M.

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	M.W. CHANG ET AL.,: "Cytostatic gene therapy for vascular proliferative disorders with a constitutively active form of the retinoblastoma gene product" SCIENCE, vol. 267, 1995, WASHINGTON DC, US, pages 518-522, XP000609101 cited in the application see the whole document	1,7,8, 13-17, 19-21, 23-25, 27,28, 33-36, 38,39
X	L. LI ET AL., : "Expression of the SM22 alpha promoter in transgenic mice provides evidence for distinct transcriptional regulatory programs in vascular and visceral smooth muscle cells" THE JOURNAL OF CELL BIOLOGY, vol. 132, no. 5, 1 March 1996, pages 849-859, XP000609076 cited in the application see the whole document	1-5,35
X	& DATABASE EMBL/DDBJ Accession number: u36589, 28 May 1996 see abstract	2-5,35
X	H. MOESSLER ET AL., : "The SM22 promoter directs tissue-specific expression in arterial but not in venous or visceral smooth muscle cells in transgenic mice" DEVELOPMENT, vol. 122, 1 May 1996, CAMBRIDGE, UK, pages 2415-2425, XP000196601 cited in the application see the whole document	1-5,35
X	& DATABASE EMBL/DDBJ Accession number :z68618, 16 January 1996 see abstract	2-5,35
X	P.R. KEMP ET AL., : "Cloning and analysis of the promoter region of the rat SM22 alpha gene" BIOCHEMICAL JOURNAL, vol. 310, 1995, LONDON, UK, pages 1037-1043, XP000196609 see the whole document and specially figure 4	1-5,35
X	& DATABASE EMBL/DDBJ Accession number :z48607, 6 March 1995 see abstract	2-5,35
A	EP 0 666 270 A (SQUIBB BRISTOL MYERS CO) 9 August 1995 see page 3, line 6-29	7,8,27, 28,44,46

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 11506 A (ARCH DEV CORP) 26 May 1994 cited in the application see the whole document	9,16-18, 24,25, 29,34, 36,38, 39,45, 47-49, 51,52
A	WO 96 26742 A (UNIV CALIFORNIA) 6 September 1996 see abstract	9,10, 13-21, 29, 47-49,51
A	WO 96 00006 A (UNIV PITTSBURGH) 4 January 1996 see the whole document, specially pages 6-12, 23-33	10, 13-16, 18-21, 29,30, 47-49, 52,53
A	WO 94 13824 A (UNIV PARIS CURIE) 23 June 1994 see page 3, paragraph 6 - page 4, paragraph 2	11,31
E	WO 97 35974 A (PASTEUR INSTITUT ;UNIV PARIS) 2 October 1997 see the whole document	1-5, 7-11, 13-25, 27-31, 33-36, 38-53

INTERNATIONAL SEARCH REPORT

[redacted] patent family members

[redacted] Application No
[redacted] 97/16204

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0666270 A	09-08-95	US 5625031 A	29-04-97
		CA 2140379 A	09-08-95
		JP 7316196 A	05-12-95
WO 9411506 A	26-05-94	AU 5609394 A	08-06-94
		CA 2149771 A	26-05-94
		EP 0668913 A	30-08-95
		JP 8506008 T	02-07-96
WO 9626742 A	06-09-96	AU 5028796 A	18-09-96
		AU 5457096 A	31-10-96
		CA 2188575 A	06-09-96
		EP 0760682 A	12-03-97
WO 9600006 A	04-01-96	US 5658565 A	19-08-97
		AU 2869095 A	19-01-96
		CA 2193827 A	04-01-96
		EP 0769903 A	02-05-97
		ZA 9505210 A	21-02-96
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